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EXAMINER
TURNER, SHARON L

ART UNIT	PAPER NUMBER
1647	17

DATE MAILED: 07/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/865,294	WANG, CHANG YI	
	Examiner	Art Unit	
	Sharon L. Turner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *04 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-80* is/are pending in the application.

4a) Of the above claim(s) *3,11,13,23,31,33 and 41-80* is/are withdrawn from consideration.

5)☒ Claim(s) *10 and 30* is/are allowed.

6)☒ Claim(s) *1,2,4-8,12,14-22,24-28,32 and 34-40* is/are rejected.

7)☒ Claim(s) *9 and 29* is/are objected to.

8)☒ Claim(s) *1-80* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 May 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The Examiner notes that SEQ ID NO:51 is deemed to be free of the prior art and is enabling as a T helper cell epitope as evidenced in the specification. In a telephone inquiry conducted by the Examiner on June 11, 2003 with Applicant's Representative Maria Lin, Applicant's Representative declined an expedited allowance of claims directed to constructs comprising SEQ ID NO:51 in favor of a first action on the merits. Accordingly the following Office Action has been issued. (SEQ ID NO's 71-74) comprise SEQ ID NO:51.

Sequence Requirements

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

It is further noted that the invention of elected claims 1-40 are drawn to various peptide sequences that are separated by gaps with different gap lengths depending upon the presence or absence of an optional spacer element and/or of analogous sequences. In particular claim 1 specifies that the peptide immunogens are of about 20-100 amino acids long. Thus, what is claimed appears to be multiple peptide sequences made up of one or more noncontiguous segments. Accordingly, the claims

do not comply with 37 CFR § 1.822(e) which states that "[a] sequence that is made up of one or more noncontiguous segments of a larger sequence or segments from different sequences shall be presented as a separate sequence". Applicant would need to provide a substitute computer readable form (CRF) copy of a "Sequence Listing" which includes all of the sequences recited in the claims of the instant application and encompassed by these rules, a substitute paper copy of that "Sequence Listing", an amendment directing the entry of that paper copy into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. §§ 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). The instant specification and/or claims will also need to be amended so that they comply with 37 C.F.R. § 1.821(d) which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification and claims wherever a reference is made to that sequence. See M.P.E.P. 2422.04. As an alternative Applicant's may wish to consider the applicability of a generic sequence that adequately represents a common structural core that exhibits the same function.

It is noted that the prior art search has only been carried out to the extent of sequences of SEQ ID No's: 51, 67 and 73 as elected. A search for the full scope of the generic claim at this juncture is impossible given the noncontiguous segments, various gaps and/or linkers and by analogs or variants.

Election/Restriction

3. Applicant's election with traverse of Group I, claims 1-40 in part to the extent of SEQ ID NO's: 51 and 67 linked via (α, ε-N)-Lys represented as SEQ ID NO:73 in Paper No's. 8 (10-30-02) and 11 (3-4-02) is acknowledged. Applicants assert that claims 1-2, 4-10, 12, 14-22, 24-32 and 34-40 read on the elected species. However, it is noted that claim 31 depends from non-elected claim 11. Thus, it is deemed that claims 1-2, 4-10, 12, 14-22, 24-30, 32, 34-40 in part read on the elected species. The traversal is on the ground(s) that the groups are sufficiently related and linked such that examination of the multiple groups and species should be together in a single application. This is not found persuasive because as claimed the products and product compositions are distinct as the encompassed structures lack definitive common structure as claimed. Moreover the methods as claimed differ in effects; i.e., the methods of Group II represent methods of prevention or treatment whereas the methods of Group III are drawn to the production of antibodies. The products, compositions and methods are separately classified evidencing their divergent status in the art. Moreover a search for any one of the different compositions or methods is not coextensive with any other and therefore the search and examination of the multiple inventions in a single application bears undue burden upon the Examiner. Claims that are deemed to be allowable and properly linking may be subject to rejoinder.

The requirement is still deemed proper and is therefore made FINAL.

4. Claims 3, 11, 13, 23, 31, 33 and 41-80 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and species,

there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8 and 11.

Claim Objections

5. Claims 1-2, 4-9, 12, 14-22, 24-29, 32 and 34-40 are objected to as reciting an improper Markush Group. M.P.E.P. 803.02 states that:

"Since the decisions in In re Weber **,198 USPQ 328 (CCPA 1978); and In re Haas, 198 USPQ 334 (CCPA 1978), it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention, In re Harnish , 631 F.2d 716, 206 USPQ 300 (CCPA 1980); Ex Parte Hozumi , 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility."

In instant case, claims 1, 9 and 12 set forth a super-genus or a group of compounds that are multiply generic, i.e., the claims fail to set forth a single defined genus that shares a common core structure. As the compounds differ in common structure and are capable of different use and effects based on that core structure, the claims as set forth lack unity of invention. While some of the elements are shared the peptide immunogens claimed do not to conform to a common core sequence that sets forth the specific residues that are required from those that are variable. Accordingly, the elements are not shared and a search conducted for any one element fails to reveal all pertinent prior art to any other element. Claims 2, 4-8, 14-22, 24-30, 32 and 34-40 depend from claims 1, 9 or 12 and thus share the multi-generic nature of the claims. However, it is noted that particular sequences may share sufficient structure such that applicants may provide for a generic claim (formula) that adequately represents or links particular core embodiments. Correction is required.

6. Claims 1-2, 4-8, 12, 14-22, 24-28, 32 and 34-40 are objected to because of the following informalities: The claims are objected to as reciting or depending from claims reciting multiple peptide sequences that do not comply with the Sequence Rules. The non-contiguous structures do not comply as set forth above. Appropriate correction is required.

Claim Rejections - 35 USC § 101

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 1-2, 4-8, 12, 14-22, 24-28, 32 and 34-40 are rejected under 35 U.S.C. 101 because the claimed invention is directed in part to non-statutory subject matter. The peptide immunogens claimed do not necessarily reflect the hand of man and potentially read on a product of nature. Amendment to "An isolated peptide immunogen" or "A synthetic peptide immunogen" is suggested. Claims 10 and 30 are drawn to the preferred election/embodiment. The specific peptide is not naturally occurring and thus is not included in the rejection. Claims 9 and 29 are similarly drawn to non-naturally occurring amino acids as depicted in Table 4. However, the claims have not been examined to the extent of the additional SEQ ID NO's for the reasons set forth above. Alternatively, amendment or evidence that the scope of the claims does not reflect or read on a product of nature would obviate the rejection.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-2, 4-8, 12, 14-22, 24-28, 32 and 34-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification and claims describe multiple polypeptide constructs wherein the constructs optionally contain particular elements. The elements include independent amino acids, N-terminal fragments of beta amyloid peptide, linking groups, and T helper cell epitopes. Minimally, the peptide comprises an N-terminal fragment of beta amyloid peptide fused with a T helper cell epitope. In claim 1 and dependent claims thereof the T helper cell epitope must be selected from SEQ ID NO's:1-64. However, in claim 12 and dependent claims thereof the sequence may be either selected from SEQ ID NO's:1-64 or may be an "immune enhancing analog thereof". In claims 1, 12 and dependent claims thereof the N-terminal fragment of beta amyloid may be from 10-28 residues wherein the N-terminal first amino acid residue is included or the N-terminal fragment may be an "immunologically functional analog" thereof. Thus in claim 1 and dependent claims thereof, only the T helper cell epitope is fixed while the N'-terminal fragment is structurally variable. In claim 12 and dependent claims thereof,

neither the T helper cell epitope nor the N-terminal fragment is fixed. While the T helper SEQ ID NO's and beta amyloid peptide structure provide particular information as to the partial structure or sequence of the claimed peptide immunogens, the "immunologically functional analogs" or "immune enhancing analogs" lack any particular structure within the claims. Thus, in claim 1 and dependent claims thereof the claim minimally receives structural guidance only as to a particular T cell epitope whereas in claim 12 and dependent claims thereof the claims minimally receive no fixed structural guidance and the peptide may be completely variable.

While the "immunologically functional analog" or "immune enhancing analog" appear to be recitations of function, the specification fails to define or provide guidance as to the particular immunologic or immune enhancing function that is to be provided. For example, Applicants could be referring to T-cell killing, proliferation, cytokine production or the stimulation of a B-cell response amongst any number of peptide immunogens, antigens or epitopes. Yet the specification does not describe the particular function of the peptide immunogen's elements. Moreover, the functional recitations lack description or guidance as to those residues that provide for or are required for the function of an "immunologically functional analog" or an "immune enhancing analog" as claimed.

Thus, the claims as written encompass polypeptide structures comprising various fragments and homologues that vary substantially in length, amino acid composition, function and effects. The instant disclosure of particular sequences that provide for a single element of the claimed peptide immunogent fail to adequately describe the scope

of the claimed genus, encompassing a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606."

A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The same may be applied to peptides. While the specification provides a basis for particular elements within a proposed genus the elements are so loosely described and variable that the artisan cannot discern a distinct genus amongst the various members. No particular and definitive structure reliably describes a group of compounds with the same function.

The artisan recognizes that protein function cannot be reliably predicted from protein sequence, see in particular Skolnick et al., Trends in Biotech., 18:34-39, 2000. Given the unpredictability of homology comparisons, and the fact that the specification provides limited description and/or evidence that the sequences as encompassed by the claims are indeed species of a claimed genus, i.e., that share common structure and function, it cannot be established that a representative number of species have been disclosed to support the genus claims. No particular activity is set forth for the additional sequences. The specification further sets forth limited guidance to a proposed consensus sequence that is definitive of the genus. There is no correlation or nexus provided between possession of any particular structural feature and conservation of a common function.

11. Claims 1-2, 4-8, 12, 14-22, 24-28, 32 and 34-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a T helper cell epitope of SEQ ID NO:51 and for stimulating antibody responses with the particular peptide immunogens claimed, does not reasonably provide enablement for peptide immunogens drawn to immunologically functional analogs and to immune enhancing analogs thereof wherein the function that is to be conserved is not specified. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claim limitations.

The skilled artisan readily recognizes that protein chemistry is an unpredictable area of biotechnology. Proteins with replacement of single amino acid residues may

lead to both structural and functional changes in biological activity and immunological recognition, see in particular Skolnick et al., Trends in Biotech., 18(1):34-39, 2000. For example, Jobling et al, Mol. Microbiol., 1991, 5(7):1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which produce proteins that differ in native conformation, immunological recognition, binding and toxicity, thus exemplifying the importance of conserved structural components to both biological function and immunological recognition. The skilled artisan also recognizes that immunological responses depend upon the structural characteristics (conformation) of the particular protein (amino acid sequence) targeted.

Instant claims are directed to various peptide immunogens. While the artisan recognizes that virtually any peptide may be engineered so as to stimulate an immune or antigenic (antibody) response, the artisan cannot predict those peptide immunogens that may provide for a particular protective response, i.e., that are for example immunologically functional analogs or immune enhancing analogs thereof. The specification fails to disclose the immunological function or enhancement that is required. Applicants may be referring to the stimulation of antibodies, T-cells or some other response that is not specified. The specification teaches that the peptide immunogens claimed are useful for the prevention and treatment of Alzheimer's disease. However, the specification fails to teach that the administration of the particular polypeptides claimed are able to reduce beta-amyloid levels within the brains of Alzehimer's patients.

Instant specification does not enable the broad scope of the claims which encompass a multitude of analogs or equivalents because the specification does not teach which residues can or should be modified such that the polypeptides retain sufficient structural similarity to evoke a requisite response. The specification provides essentially no guidance as to which of the nearly infinite possible choices is likely to be successful and the skilled artisan would not expect functional conservation among homologous or variable sequences. Thus, applicants have not provided sufficient guidance to enable one skilled in the art to make and use the claimed derivatives in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

While applicants are enabled for the stimulation of an antibody response with particular peptide immunogens, the claims are not so limited.

In view of the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue experimentation to make and use the claimed invention.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 1-2, 4-8, 12, 14-22, 24-28, 32 and 34-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The metes and bounds of the claims are indefinite with respect to the recitations of peptide immunogens comprising Th epitiopes that are immune enhancing analogs thereof or beta amyloid fragments that are immunologically functional analogs thereof. In particular, the skilled artisan recognizes a multitude of immune enhancing and immunological functions including but not limited to antibody respsonse, T cell responses, cell killing, cytokine production, lymphoprliferation. However, the specification fails to provide guidance as to which of the art recognized activities are intended to be conserved amongst the Th epitopes and N-terminal fragments of beta amyloid or their analogs. Thus, the artisan can neither discern nor test for the peptide immunogens encompassed by the claims. Clarification of the scope is required.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 12 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by McMichael and Kline, US Patent No. 5,753,624, May 19, 1998.

McMichael et al., teach a method for alleviating (or treating) the symptoms of disease states associated with amyloid plaque formations, such as Alzheimer's disease, via administration of an effective amount of amyloid protein, see in particular claim 1 and column 7, lines 39-52 and columns 9-16, Application of Materials and Methods of the invention to the treatment of Alzheimer's and related diseases. In particular, the invention includes where the amyloid protein is amyloid beta protein or the first 28 residues of amyloid beta, see in particular claims 2-8. In Examples 1-6, the patients showed improvements in cognitive function as measured by the mini-mental state examination and other measures, see in particular column 10, lines 3-10. The peptides are suitable peptide immunogens of the formula of claim 12 as the (A) element is not required where n=0, element (B) is not required where o=0, the element (Th) is an immune enhancing analog and the N-terminal fragment for example of 1-28 is provided and is an immunologically functional analog and where X is a C-terminus α-COOH carboxy terminus of the amino acid peptide. Thus, the reference teachings anticipate the claimed peptide immunogen.

16. Claims 12 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Kumar et al., In vitro Cellular & Developmental Biology. Animal, 2000 Feb. 36(2):81-87.

Kumar et al., teach antibody produced via immunization with a synthetic peptide of the first 14 amino acids of beta amyloid, corresponding to elected SEQ ID NO:67. The synthetic peptide produces an antibody in rabbits capable of detecting beta-amyloid plaques as exemplified in Kumar, see in particuar, pp. 82, column 2, Immunostaining and Figures 1-6. Thus, Kumar evidences the suitability of AB1-14 as a B cell eptiotpe

capable of stimulating antibody for the detection of Alzheimer's plaques in vivo. In particular, the invention includes where the amyloid protein is amyloid beta protein or the first 14 residues of amyloid beta and antibody is produced thereto. The peptides are suitable peptide immunogens of the formula of claim 12 as the (A) element is not required where n=0, element (B) is not required where o=0, the element (Th) is an immune enhancing analog and the N-terminal fragment for example of 1-14 is provided and is an immunologically functional analog and where X is a C-terminus α-COOH carboxy terminus of the amino acid peptide. Thus, the reference teachings anticipate the claimed peptide immunogens.

Claim Rejections - 35 USC 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 1-2, 4-8, 12, 14-22, 24-28, 32, and 34-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al., WO99/66957, December 29, 1999, Wang et al., WO99/66952, December 29, 1999, Behrouz et al., J. of Gerontol., 44(6):B156-9, Nov. 1989 and , McMichael and Kline et al., US Patent No. 5,753,624 filed August 8, 1996 and issued May 19, 1998 and Kumar et al., In vitro Cellular & Developmental Biology. Animal, 2000 Feb. 36(2):81-87.

Wang et al., WO99/66957 and WO99/66952 similarly teach artificial T helper cell epitopes as immune stimulators for synthetic peptide immunogens. The synthetic peptide immunogens are suitable B cell epitope target antigens, see in particular pps. 1, '952 and '957. In particular the Wang references teach T helper cell epitopes corresponding to instant SEQ ID NO:38 deemed to be an immune enhancing analog of SEQ ID NO:51 based on 87% conservancy and conserved function with instant SEQ ID NO:51 T helper cell epitope, see in particular Wang et al., '952 and '957 Tables 1, pp. 29 and 54, respectively. The Wang references similarly teach the use of an optional spacer ε-N-Lys- and the optimal peptide immunogen lengths of about 20-100 amino acids in length, see in particular '952 and '957 claims. Additionally, the Wang

references teach pharmaceutical compositions with suitable adjuvants including ISA51, ISA720, DDA, MPL, QS21 etc., see in particular pp. 19 of '952 and pp. 23 of '957.

Wang et al., '952 and '957 fail to teach the claimed peptide immunogens wherein the peptide immunogen part of the molecule is an N-terminal fragment of beta amyloid consisting of from 10-28 amino acid residues in length, SEQ ID NO:65, 67 or a immunologically functional analog thereof as claimed.

Behrouz et al., teach polyclonal antibodies to synthetic peptide beta amyloid protein residues 1-10, see in particular abstract. Behrouz evidences that the Abeta1-10 peptide is a suitable B cell epitope as the epitope is sufficient to stimulate antibodies reactive with Alzheimer brain tissue. The antibodies stained senile plaques and angiopathic vessels specifically and did not cross react with Tau.

McMichael et al., teach a method for alleviating (or treating) the symptoms of disease states associated with amyloid plaque formations, such as Alzheimer's disease, via administration of an effective amount of amyloid protein, see in particular claim 1 and column 7, lines 39-52 and columns 9-16, Application of Materials and Methods of the invention to the treatment of Alzheimer's and related diseases. In particular, the invention includes where the amyloid protein is amyloid beta protein or the first 28 residues of amyloid beta, see in particular claims 2-8. In Examples 1-6, the patients showed improvements in cognitive function as measured by the mini-mental state examination and other measures, see in particular column 10, lines 3-10. Thus McMichael teaches and evidences that the 1-28 fragment is a suitable B cell epitope

capable of stimulating antibody and for the stimulation of an adequate immune response for the treatment of Alzheimer's Disease.

Kumar et al., teach antibody produced via immunization with a synthetic peptide of the first 14 amino acids of beta amyloid, corresponding to elected SEQ ID NO:67. The synthetic peptide produces an antibody in rabbits capable of detecting beta-amyloid plaques as exemplified in Kumar, see in particuar, pp. 82, column 2, Immunostaining and Figures 1-6. Thus, Kumar evidences the suitability of AB1-14 as a B ceil eptiotpe capable of stimulating antibody for the detection of Alzheimer's plaques in vivo.

Based upon the teachings of Behrouz and McMichael, the skilled artisan would know that peptide immunogens comprising the N-terminal fragments of the beta amyloid in the region of beta amyloid 1-10 or 1-28 sequence would be suitable to stimulate an immune response for the purpose of obtaining antibodies capable of detecting Alzheimer's plaques in patients. In addition, Kumar expemplifies such abilities with the preferred embodiment where the N-terminal portion is specifically that of SEQ ID NO:67, beta amyloid residues 1-14. Moreover based upon the cumulative teachings of Wang et al., '952,'957 and Behrouz and McMichael the skilled artisan would be further motivated to use the improved process of stimulating specific antibodies via the use of T helper cell epitope peptides to improve the antibody response and specificity effected in patients. One of skill in the art would have been motivated to modify such administration for the purpose of obtaining antibodies for the specific detection of Alzheimer's plaques, for enhancing an immune response recognized in the art to be protective and to provide treatment for Alzheimer's Disease in patients. One of skill in

the art would have expected success given the exemplifications of each of the references with respect to the particular peptides and the effects noted for enhancing the immune response, detecting Alzheimer's plaques and preventing or treating Alzheimer's disease. Thus based upon the cumulative reference teachings, the claimed peptide immunogens would have been obvious to the skilled artisan at the time the invention was made.

Status of Claims

19. Claims 10 and 30 are allowed.

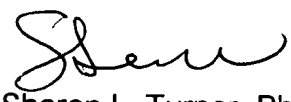
20. Subject matter directed to peptides comprising SEQ ID NO:51 is free of the prior art.

21. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Applicants and their attorneys or agents are required to conduct their business with the Patent and Trademark Office with decorum and courtesy, see in particular MPEP, Patent Rules § 1.3.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.



Sharon L. Turner, Ph.D.
June 30, 2003